action has been pictured[14] as progressing through the intermediate phenyldimethyl carbanion, $C_6H_5C(CH_3)_2^-$, which adds to ethylene to form a new carbanion, $C_6H_5C(CH_3)_2CH_2CH_2^-$, which, in turn, abstracts a tertiary hydrogen from cumene to maintain the chain, while forming the final hydrocarbon, t-amylbenzene. With sodium reagents however, this alkylation should be on the nucleus instead of the tertiary carbon, because the carbanion is on the nucleus. Alkylation of p-cymene also should occur at the methyl group, because that position alone is metalated by either sodium[9b] or potassium[15] reagent; yet alkylation occurred at the isopropyl group.[14a] The above mechanism, therefore, can scarcely be correct.

The facts are beautifully accommodated, however, to the view of biradical activity along the lines used to explain alfin catalysis.[3] At first, ethylene coordinates with the cation of the promoter, Na^+–R, to give the complex salt, $[C_2H_4{\rightarrow}Na]^+$–$R$. Next, dissociation to two radicals, $Na\cdot$ and $\cdot R$, occurs. Then the carbyl removes the tertiary hydrogen from cumene to give $C_6H_5C(CH_3)_2\cdot$ in a process typical for radicals, while atomic sodium converts the adjacent olefin into an anion-radical, Na^+–$CH_2CH_2\cdot$. Finally, the two radicals unite to form an end salt product, Na^+–$CH_2CH_2(CH_3)_2CC_6H_5$, which serves as the promoter to start the cycle again and to form t-amylbenzene. The several steps are closely consecutive or almost simultaneous. In its fine detail the process provides good evidence for radial pair (atomic metal and carbyl)[3,8] activity rather than serves as an example of carbanion chemistry.

EXPERIMENTS

Metalation of cumene. In three experiments amylsodium was prepared in heptane from 1 g. atom of sodium sand and 0.5 mole of amyl chloride in the customary way.[4,12] To one preparation a mole of cumene was added. To a second was added one mole of cumene and 1.5 mole of triethyl amine which previously had been dried over amylsodium. To the third was added 4 ml. (0.22 mole) of water, followed by one mole of triethyl amine and 0.5 mole of cumene. Each mixture was heated quickly to 70° and kept there for 3 hr., with stirring at 10,000 r.p.m. After being cooled to room temperature, the contents were forced into a 4-liter Erlenmeyer flask filled to a quarter of its depth with powdered carbon dioxide. The reaction flask was rinsed twice with 200 ml. of heptane which likewise was carbonated.

The next day 300 ml. of water was added to dissolve the salts. When both layers had cleared the hydrocarbon portion was separated and extracted with 50 ml. of 10% aqueous sodium hydroxide, followed by 50 ml. of water. Next, the combined aqueous layer and extracts were extracted with four 150-ml. portions of ether, after which the aqueous portion was acidified with 50% (by volume) sulfuric acid. A white precipitate which appeared and the solution were extracted with four 150-ml. portions of ether. The ether

extract was dried over Drierite, filtered and made up to 500 ml., from which a 5-ml. aliquot was titrated in order to determine the total carboxylic acid.

The ether solution was evaporated to about 50 ml. and 200 ml. of petroleum ether was added. Overnight, 5-iso-propylisophthalic acid precipitated. It was washed, dried, weighed and recorded as dimetalated product. After being crystallized from ethanol-water, it was identified by its neutralization equivalent, 107 (calcd. 104), its melting point, 282–285° (lit.[16] 285°), the melting point of its dimethyl ester, 64–65° (lit.[11] 64–65°), and a mixed melting point with an authentic sample.

The petroleum ether decantate was evaporated to one-half its volume and cooled. The first crop of crystals had the correct neutralization equivalent for p-isopropylbenzoic acid and melted at 115–117° (lit.[9] 116–118°). Its amide melted at 152–153° (lit.[17] 153°).

The remaining petroleum ether in the mother liquor was evaporated and the acid residue was fractionated to remove caproic acid (b.p. 60°/4 mm.). An aliquot (1.5 g.) from the acid residue was oxidized with chromium trioxide according to the method developed by Bryce-Smith and Turner[5] for determining the amount of m-isopropylbenzoic acid and α-phenylisobutyric acid.

The yields calculated from these operations, with appropriate allowances for all samples removed, are recorded in Table I. They show that triethyl amine, and particularly triethyl amine with sodium hydroxide, decreased the amount of metalation of cumene. The loss is accounted for as decomposition of amylsodium,[1,8] although the formic acid was not measured. No product from metalation at the alpha carbon atom was observed.

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Transmetalation of Thiophene by the Ethylsodium-Diethylzinc Complex[1]

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In general, organosodium compounds will transmetalate with hydrocarbons if they can form an organometallic corresponding to a stronger acid. However, Morton and co-workers[3] have shown that this rule is not followed invariably (for example: Amylsodium metalates t-butylbenzene predominantly in the *para* position, but in the presence of sodium alcoholates *meta* metalation occurs preferentially). The mechanism of transmetalation is still the subject of discussion.[4] Its elucidation is made more difficult because sodium alkyls are insoluble in hydrocarbon solvents. Steric factors and

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changes in the polarization of bonds may create surface effects on the insoluble sodium alkyl aggregates which overrule the acidity influence.

A homogeneous system should greatly simplify a study of transmetalation reactions. As the complex formed by ethylsodium and diethylzinc is soluble in benzene,[5] its use as a metalating agent was attempted. For convenience a solution of the complex in diethylzinc was chosen which contained ethyl sodium and diethylzinc in a ratio of 1:1.84 and which could easily be prepared according to Hein.[6]

The complex, dissolved in benzene or 1,2-dimethoxyethane, metalated fluorene but not triphenylmethane at room temperature. Thus, the activity of the complex, relative to the hydrocarbon acidity series,[7] was intermediate between that of ethylsodium and diethylzinc. Complex formation does, therefore, decrease the activity of ethylsodium.

The complex seemed to be stable at room temperature, as a 2% solution in styrene did not give any visible signs of polymerization, which would be indicative of the presence of radicals according to Ziegler.[8] When the solution was warmed to 60°, a red color developed and the styrene was polymerized violently. This is in agreement with the thermal instability of the complex as reported by Wanklyn[5] and by Carothers and Coffman.[9] A transmetalation by the complex was attempted with thiophene which according to Schick and Hartough[10] cannot be metalated by sodium alkyls except in the presence of mercury, although Morton[11] has claimed lately that thiophene can be dimetalated by amylsodium in presence of sodium t-amylate.

On addition of the complex to thiophene a clear solution resulted, gas development began, and later two layers formed. After several hours the mixture was carbonated and thiophene-2-carboxylic acid was isolated in a 55% yield. The acidity rule predicted metalation by alkylsodium rather than by the less reactive complex. The separation of the solution into two phases suggested the formation of a compound of the complex with thiophene, which seemed to be responsible for the unexpected course of the reaction.

EXPERIMENTAL

Metalation of Fluorene by the Ethylsodium–Diethylzinc Complex. Fluorene, 0.248 g. (0.00149 mole), was treated

with 0.408 g. of the ethylsodium–diethylzinc complex (containing 0.00145 mole NaC_2H_5) in 40 ml. of dry benzene under nitrogen at room temperature. Gas bubbles developed, and the solution became reddish orange. After 30 minutes the reaction mixture was carbonated by pouring into Dry Ice and ether, and worked up to give 0.125 g. (41.2%) of fluorene-9-carboxylic acid, m.p. 221–223°. A mixed melting point with an authentic sample of fluorene-9-carboxylic acid was not depressed.

The result was the same with 1,2-dimethoxyethane as solvent.

Diethylzinc did not affect fluorene under these conditions.

Reaction of the Ethylsodium–Diethylzinc Complex with Styrene. The complex (0.534 g., containing 0.0019 mole NaC_2H_5), dissolved in 20 ml. of freshly distilled styrene and kept under nitrogen at room temperature, gave no indication of reaction after 30 minutes. The flask was then heated to 60–65° with a water bath. At this temperature the solution became dark red and the styrene polymerized violently.

Metalation of Thiophene by the Ethylsodium–Diethylzinc Complex. The complex (2.99 g., containing 0.0106 mole NaC_2H_5) was dissolved in 25 ml. of dry thiophene under nitrogen at room temperature. Gas development was noted. After about 10 minutes a second phase, from which the gas bubbles appeared to originate, separated. After 4 hr. the reaction mixture was carbonated by pouring into Dry Ice and ether. 0.75 g. (55%) of thiophene-2-carboxylic acid was isolated, m.p. 127–128°. No depression of a mixed melting point with an authentic sample of thiophene-2-carboxylic acid was observed.

No reaction was observed between thiophene and diethylzinc under the same conditions.

Synthesis of 4(5)-Imidazolylacetylcholine and 2-Pyridylacetylcholine

FRANK H. CLARKE AND C. M. WATNICK

The isolation from natural sources of β-[4(5)-imidazolyl]-acryloylcholine (murexine)[1,2] as well as the apparent isolation of 4(5)-imidazolylacetylcholine[3] from mammalian brain has led to numerous studies of the pharmacology of these choline esters as well as β-[4(5)-imidazolyl]-propionylcholine (dihydromurexine[4,5]). These compounds are potent ganglionic stimulants and neuromuscular blocking agents.[4] In order to study the pharmacology of

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